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14. ABSTRACT
This project seeks to understand the role that aberrant eye-movements and gaze patterns in ASD may play in the organization of visual processing mechanisms and how the basic retinotopic maps in early visual cortices may develop atypically as a consequence of these anomalies in gaze. The underlying premise is that basic sensory processing anomalies may be related to what at first blush appear to be social deficits – e.g. not looking a peer in the eye during communication. Work using high-density event-related potentials (ERPs) has revealed atypical visual adaptation functions in Autism, again pointing to basic sensory processing anomalies in this population. Our research team is developing precise retinotopic mapping procedures using functional neuroimaging, procedures appropriate for detailed mapping of early visual maps in the often challenging-to-test ASD pediatric population.

15. SUBJECT TERMS
Autism, Visual Adaptation, Retinotopy, Social Communication, Eye-movements, fMRI, EEG, ERP.

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Introduction

Impairments in social interaction are a hallmark symptom of Autism, and the lack of appropriate eye-contact during interpersonal interactions is an oft-noted feature of this population. We and others have observed that it is not only during social interactions that individuals with an ASD show aberrant fixation patterns, raising the possibility of much more fundamental deficits in the sensory-motor integrations necessary to accurately move one's gaze around. Using electrophysiological techniques, our group has shown that reduced accuracy in oculomotor control leads to changes in cortical representations of visual space (Frey et al., 2013). The current project was aimed at developing understanding of how eye-movement anomalies in ASD might relate to sensory-perceptual alterations and social difficulties in this population. We employed both high-density electrophysiology and functional neuroimaging measures in conjunction with measures of eye-movement precision to assess fundamental visual processing in ASD. We developed more accurate measures to use functional imaging to map out, with high fidelity, the retinotopic representations of visual space along the visual processing hierarchy. In this final progress report, we detail work on the two main experiments in the project. The first details electrophysiological results from an experiment using high-density electrophysiology to assay visual sensory adaptation functions in the hierarchically early regions of the visual processing hierarchy in ASD. The second details our work to establish and successfully record functional imaging measures of the retinotopic representation of space in ASD.

Keywords

Autism, Visual Adaptation, Retinotopy, Social Communication, Eye-movements, fMRI, EEG, ERP.

Accomplishments

Subtask 1: Program and test experimental paradigms.

1) Experimental paradigms to test saccade accuracy and saccade adaptation were developed and recordings from both neurotypical control and ASD participants were made.
2) A paradigm to assess visual sensory processing, specifically visual adaptation functions to repeated checkerboard stimuli was implemented. Efforts to develop a retinotopic visual-evoked potential task that children with an ASD could easily execute were not successful.
3) After a considerable initial period of technology development, we successfully implemented a sensitive assay of retinotopic mapping in early visual cortical regions using functional magnetic resonance imaging in both neurotypical controls and ASD participants.

Subtask 2: Record visually guided saccade tasks and eye-movements on social stimuli.

A paradigm to test visually guided saccade adaptation was developed and piloted successfully in individuals with an ASD. Figure 1 provides an example of differences we have observed. On the left is an example of saccade amplitude adaptation in a typically developing (TD) participant. After executing a series of saccades to a target location (left of the vertical line) adaptation trials are started. This involves moving the target in by 3 degrees of visual angle while the participants eyes are “in flight” to the original target location – i.e. while the participant is functionally blind. Over the course of ~30 adaptation trials, saccade amplitude systematically declines, reducing the imposed visual error. On the right are the results of a similar session with an ASD subject. Here the control movements are significantly hypometric and the endpoint variability is higher than in the TD subject. After adaptation trials begin, there is little or no change in saccade amplitude over the 70 adaption trials presented. We have now collected saccade adaptation data in cohorts of 16 typically developing individuals and 10 ASD participants on a variant of the saccade adaptation task. Data analyses are in process.

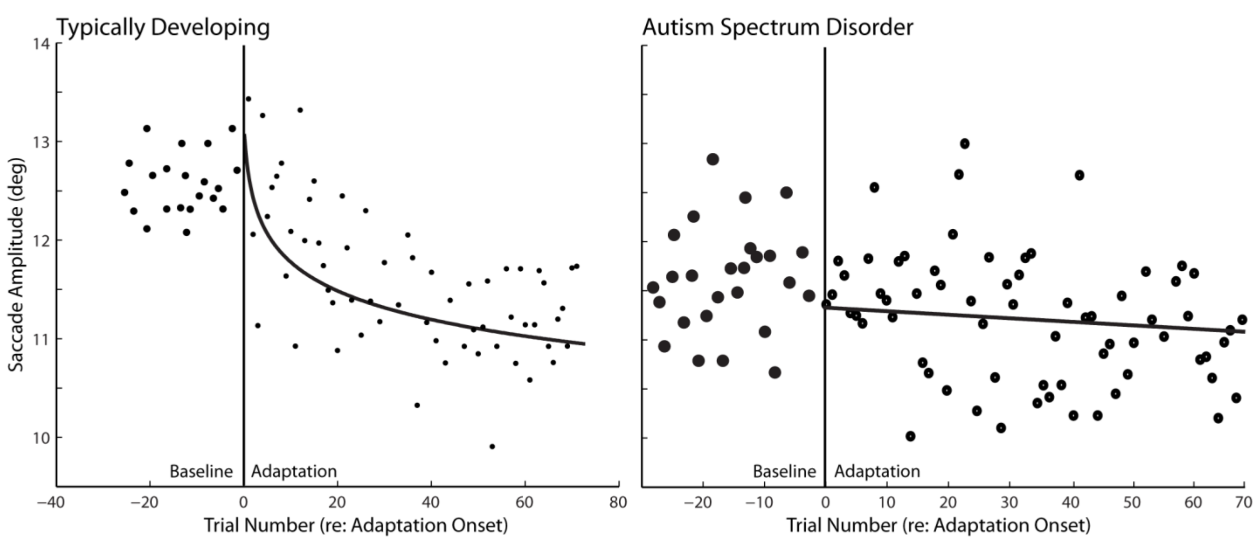

Figure 1. The left panel shows saccade adaptation data from one typically developing participant with the characteristic shortening of saccade amplitude to targets that have been moved nearer to central fixation. The right panel shows data form one ASD participant who shows no such shortening.

Subtask 3: Obtain social skill rating scale measures for all participants.

Social skills data are obtained for all participants with an ASD entering studies at the Cognitive Neurophysiology Laboratory as a routine matter.

Subtask 4: Record electrophysiological measures of visual processing

Atypical visuo-sensory representations in children with an autism spectrum disorder as assessed by high density electrical mapping. Sensory processing issues are prevalent in the autism spectrum (ASD) population, and sensory adaptation can be a potential biomarker - a measurable difference in neuronal activity that is unique for that clinical population, such as hypo- and hyper-sensitivity to sensory stimulation in the ASD population, or those at risk. Sensory adaptation is a reduction in response amplitude to repeated presentations of a stimulus, which likely represents a filter for redundant sensory stimulation. For this reason, we compared the visual evoked potentials (VEP) of children on the autism spectrum (N=24) with those of neurotypical controls (N=48). In a continuous block paradigm, we used checkerboard patterned stimuli presented continuously with varying inter-stimulus intervals (ISI) of 200 milliseconds (ms), 300 ms, 550 ms, 1050 ms, and 2550 ms, with participants instructed to maintain focus on a central fixation cross. High-density electroencephalography (EEG) was used to acquire the electrophysiological measurements, followed by epoch averaging to produce VEP waveforms. Habituation to the visual stimulus, as measured by the mean peak amplitudes, with respect to the ISI was observed at the parietal-occipital electrode sites (F (8, 72) = 5.063, p < 0.001) over the 170 to 190 ms temporal window. There was an observed diagnosis X ISI interaction effect at a latency of 140 to 160 ms between the clinical and typically developed groups (F (1, 4) = 2.846, p <.05). VEP waveforms indicate atypical sensory habituation in the ASD population. Atypical sensory habituation can be a potential biomarker for this clinical population, while further explaining differences in perception of visual sensory information between typically developed children and ASD children. We are in the process of developing a manuscript to report the results of this study.

Subtask 5: Record functional neuroimaging data

We set out to record detailed retinotopic maps of early visual cortices in ASD using functional magnetic resonance imaging. In initial pilot work, it became clear that our eye-tracking system in the magnet environment was inadequate to the task and that, in this vulnerable and movement-prone population, we could not reliably produce maps that we had confidence in (see section on Changes/Problems below). This resulted in us needing to purchase and implement a new system with much greater fidelity and accuracy, thereby delaying initial execution of this subtask. Since installation and calibration of the new eye-tracking system and development of new retinotopic mapping procedures, we have now recorded data from 13 TD and 12 ASD participants. Analyses and data collection are ongoing. Example data from our ongoing analyses are shown in the following pair of figures (Figures 2 and 3). At the time of this report submission, we are actively analyzing these data and continue to collect additional datasets to flesh out the study cohort. It is too preliminary to make any meaningful comparisons between groups at this stage.

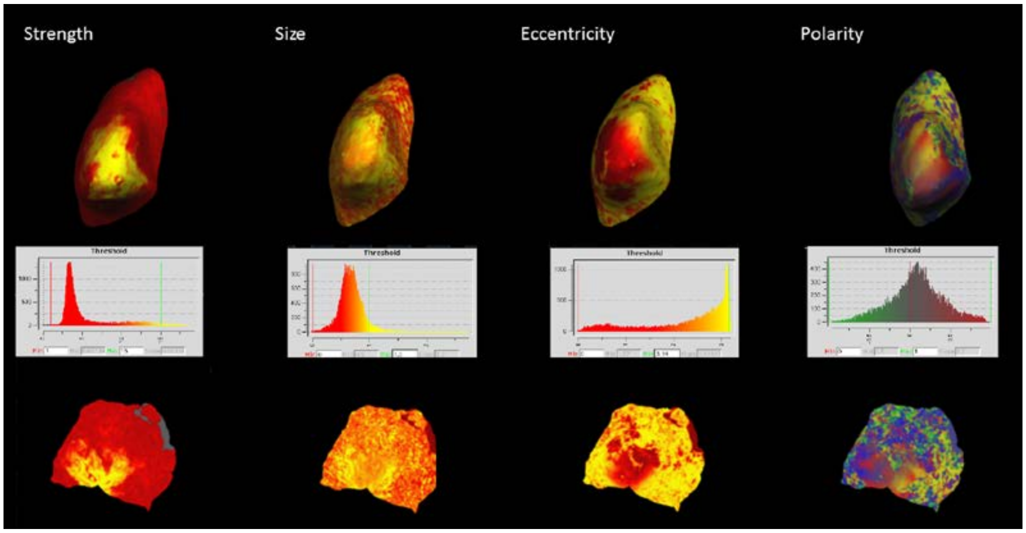

Figure 2. Data are shown from a retinotpopic mapping session for one ASD participant (Age=18 years). The top row shows a series of maps representing (from left to right), the strength of the visual response, the size of visual cortical receptive fields, responses to manipulations of visual eccentricity, and the polarity of the response (i.e. which part of the visual field is being stimulated). These maps are projected onto an "infated" 3D cortical surface. The top of each map represents dorsal visual cortex, the left is the lateral surface and the bottom is the ventral surface. The bottom series of maps represent the same data on a fllattened verison of the cortex, where the cortical manifold has been flattened by "opening" the 3D surface along the calcarine sulcus (bottom of map as indicated). The bottom of the depiction is medial visual cortex and the top is the lateral occipital lobe.

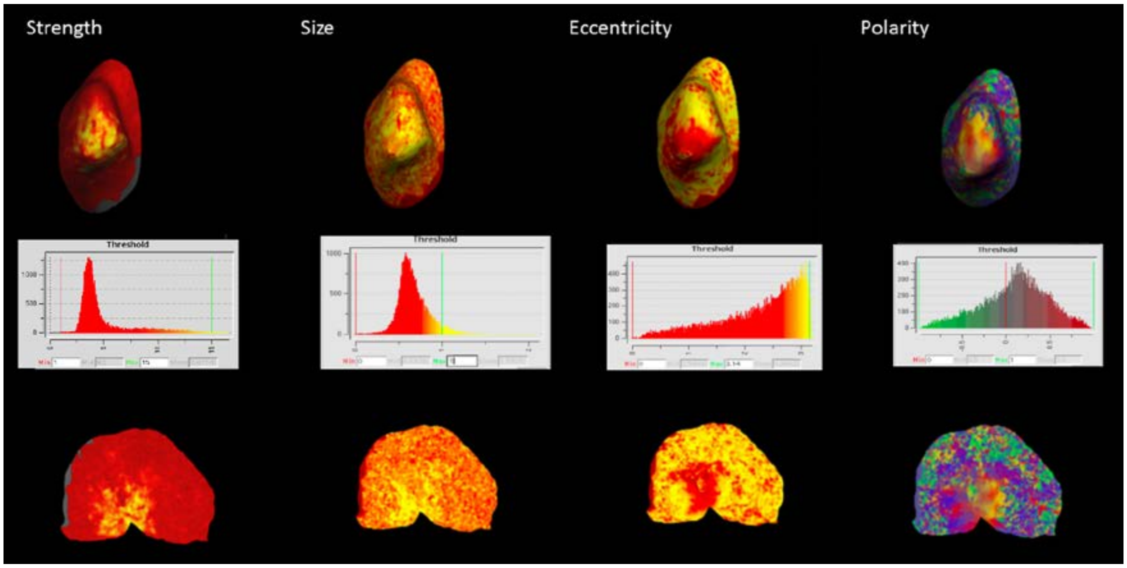

Figure 3. Data are shown from a retinotpopic mapping session for one TD participant (Age=18 years). The conventions used are exactly as those in Figure 2.

Impact
This project set out to examine the relation between atypicalities in eye-movement control and visual perception as well as social deficits in ASD. If it turns out that these constructs are related, it would provide an avenue to use simple eye-movement training in order to improve atypicalities of gaze in individuals with ASD. Our basic premise is that improved eye-movement control should affect the efficacy of visual processing, which in turn should influence social interaction. Such eye-movement training could complement existing social training techniques. Of course, it is impossible to infer directionality from a correlative measure, but it seems considerably more likely that low-level perception influences complex behaviors than the other way around. If low-level perceptual measures are not related to social deficits, then this study will provide valuable information about a condition co-occurring with ASD. For example, it allows us to examine whether the amount of eye-movement deficit relates directly to changes in visual processing. Therefore this study will lead to important insights about autism and the heterogeneity of its representation. We believe that the results of this project will provide important information to the field of autism research. Functional magnetic resonance imaging, system identification approaches for EEG, eye-tracking, and psychophysical experiments as well as combinations thereof will examine different aspects, from oculomotor control to multisensory processing to social interactions. Bringing together these separate lines of research, this project will tap into the (inter)-relation between different domains in which individuals with an ASD exhibit atypicalities and will aide in the creation of novel hypotheses regarding social deficits in ASD.

Changes/Problems
In piloting the original functional imaging design to map retinotopic regions of visual cortex in participants with an ASD, the limitations of our existing MRI–compatible eye-tracking system to adequately monitor fixation and eye-movements with the necessary level of precision became apparent. We consulted with the Dean’s office and leadership of the Gruss Magnetic Resonance Imaging Center at Einstein and in turn, purchased and installed a new and much more capable system. A VisualStim Digital System (Stereo) MRI compatible eye-tracker was acquired ($87,985) and installed using university funds and has since been used to collect data on eye-movements of participants in the scanner. This technology was essential for the investigation of brain processes underlying visual maps, especially when involving participants with ASD, and allowed for much more detailed maps of visual retinotopy as proposed in our original project.

Participants & Other Collaborating Organizations

Name: John J. Foxe, PhD
Project Role: Principal Investigator
Nearest person month worked: 2
Contribution to project: Dr. Foxe contributed to the development of experiments and analysis and interpretation of preliminary data.
Funding support: see list below (in addition to current grant)

Type: R01HD082814-01A1
Role: Co-Investigator (PI: Dr. Sophie Molholm)
Agency: NIH
Title: Sensory Integration Therapy in Autism: Mechanisms and Effectiveness

Type: Pilot Research Grant
Role: Co-PI
Agency: National Multiple Sclerosis Society
Title: Biomarkers of impaired dual-task walking abilities in multiple sclerosis: A Mobile Brain-Body Imaging (MOBI) Study

Type: NICHD P30 HD071593
Role: Associate Director of RFK Center (w/ Prof. Steven Walkley)
Agency: NICHD
Title: Support for the Rose F. Kennedy IDD Research Center

Type: The Wallace Research Foundation Grant
Role: Principal Investigator (w/ Dr. Sophie Molholm)
Agency: Wallace Research Foundation
Title: The Neurophysiology of Multisensory Integration in Sensory Processing Disorder

Type: BCS-1228595
Role: Principal Investigator (w/ Dr. Sophie Molholm)
Agency: NSF
Title: Oscillatory control of selective attention: leveraging white matter microstructure & electrophysiology

Type: Rubenstein Foundation Award
Role: Principal Investigator
Agency: Rubenstein Foundation
Title: Neurophysiological Endophenotypes of Psychiatric Disorders

Type: The Nathan Gantcher Foundation Grant
Role: Principal Investigator (w/ Dr. Sophie Molholm)
Agency: Nathan Gantcher Foundation
Title: Neural Connectivity, Multisensory Integration, and Genetic Risk Factors for Developmental Dyslexia

Type: PepsiCo
Role: Principal Investigator
Agency: PepsiCo
Title: An Electrophysiological Investigation of the Effects of Morning Nutrition on Cognitive Performance

Name:	Lars A. Ross, PhD
Project Role:	Co-Investigator
Nearest person month worked:	4
Contribution to project:	Dr. Ross managed data collection, contributed to the development of experiments, and worked with Dr. Foxe to develop data analysis strategies.
Funding support:	The Wallace Research Foundation (listed above; in addition to current grant)
Note:	Dr. Ross has been assigned the role of Co-Investigator, originally assigned to Dr. Hans-Peter Frey.